1: Science 1999 Feb 26;283(5406):1247, 1249

Comment on:
- Science. 1999 Feb 26;283(5406):1325-8

New clues to how proteins link up to run the cell.

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Publication Types:
- Comment
- News

PMID: 10084927 [PubMed - indexed for MEDLINE]

1: Genes Dev 1998 Mar 1;12(5):706-20

The essential mitotic peptidyl-prolyl isomerase Pin1 binds and regulates mitosis-specific phosphoproteins.

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Phosphorylation of mitotic proteins on the Ser/Thr-Pro motifs has been show to play an important role in regulating mitotic progression. Pin1 is a novel essential peptidyl-prolyl isomerase (PPIase) that inhibits entry into mitosis ai is also required for proper progression through mitosis, but its substrate(s) an function(s) remain to be determined. Here we report that in both human cells and Xenopus extracts, Pin1 interacts directly with a subset of mitotic phosphoproteins on phosphorylated Ser/Thr-Pro motifs in a phosphorylation-dependent and mitosis-specific manner. Many of these Pin1-binding proteins also recognized by the monoclonal antibody MPM-2, and they include the important mitotic regulators Cdc25, Myt1, Wee1, Plk1, and Cdc27. The importance of this Pin1 interaction was tested by constructing two Pin1 activ site point mutants that fail to bind a phosphorylated Ser/Thr-Pro motif in mit phosphoproteins. Wild-type, but not mutant, Pin1 inhibits both mitotic divisi in Xenopus embryos and entry into mitosis in Xenopus extracts. We have examined the interaction between Pin1 and Cdc25 in detail. Pin1 not only bi the mitotic form of Cdc25 on the phosphorylation sites important for its activ in vitro and in vivo, but it also inhibits its activity, offering one explanation f the ability of Pin1 to inhibit mitotic entry. In a separate paper, we have show that Pin1 is a phosphorylation-dependent PPIase that can recognize specifica the phosphorylated Ser/Thr-Pro bonds present in mitotic phosphoproteins. Tl Pin1 likely acts as a general regulator of mitotic proteins that have been phosphorylated by Cdc2 and other mitotic kinases.

PMID: 9499405 [PubMed - indexed for MEDLINE]